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Dramatic effect of early clopidogrel administration in reducing mortality and MACE rates in ACS patients. Data from the Swiss registry AMIS-Plus

Stauffer, Jean-Christophe ; Goy, Jean-Jacques ; Duvoisin, Nicole ; Radovanovic, Dragana ; Rickli, Hans ; Erne, Paul

Abstract: BACKGROUND: Patients who have acute coronary syndromes with or without ST-segment elevation have high rates of major vascular events. We evaluated the efficacy of early clopidogrel administration (300 mg) (<24 hours) when given with aspirin in such patients. METHODS: We included 30,243 patients who had an acute coronary syndrome with or without ST segment elevation. Data on early clopidogrel administration were available for 24,463 (81%). Some 15,525 (51%) of the total cohort were administrated clopidogrel within 24h of admission. RESULTS: In-hospital death occurred in 2.9% of the patients in the early clopidogrel group treated with primary PCI and in 11.4% of the patients in the other group without primary percutaneous coronary intervention (PCI) and no early clopidogrel. The unadjusted clopidogrel odds ratio (OR) for mortality was 0.31 (95% confidence interval 0.27-0.34; $p < 0.001$). Incidence of major adverse cardiac death (MACE) was 4.1% in the early clopidogrel group treated with 1°PCI and 13.5% in the other group without primary PCI and no early clopidogrel (OR 0.35, confidence interval 0.32-0.39, $p < 0.001$). Early clopidogrel administration and PCI were the only treatment lowering mortality as shown by multivariate analysis. CONCLUSIONS: The early administration of the anti-platelet agent clopidogrel in patients with acute coronary syndromes with or without ST-segment elevation has a beneficial effect on mortality and major adverse cardiac events. The lower mortality rate and incidence of MACE emerged with a combination of primary PCI and early clopidogrel administration.

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Dramatic effect of early clopidogrel administration in reducing mortality and MACE rates in ACS patients

Data from the Swiss registry AMIS-Plus

Jean-Christophe Stauffer, Jean-Jacques Goy, Nicole Duvoisin, Dragana Radovanovic, Hans Rickli, Paul Erne on behalf of the AMIS group

Summary

BACKGROUND: Patients who have acute coronary syndromes with or without ST-segment elevation have high rates of major vascular events. We evaluated the efficacy of early clopidogrel administration (300 mg) (<24 hours) when given with aspirin in such patients.

METHODS: We included 30,243 patients who had an acute coronary syndrome with or without ST segment elevation. Data on early clopidogrel administration were available for 24,463 (81%). Some 15,525 (51%) of the total cohort were administrated clopidogrel within 24h of admission.

RESULTS: In-hospital death occurred in 2.9% of the patients in the early clopidogrel group treated with primary PCI and in 11.4% of the patients in the other group without primary percutaneous coronary intervention (PCI) and no early clopidogrel. The unadjusted clopidogrel odds ratio (OR) for mortality was 0.31 (95% confidence interval 0.27–0.34; $p < 0.001$). Incidence of major adverse cardiac death (MACE) was 4.1% in the early clopidogrel group treated with 1°PCI and 13.5% in the other group without primary PCI and no early clopidogrel (OR 0.35, confidence interval 0.32–0.39, $p < 0.001$). Early clopidogrel administration and PCI were the only treatment lowering mortality as shown by multivariate analysis.

CONCLUSIONS: The early administration of the antiplatelet agent clopidogrel in patients with acute coronary syndromes with or without ST-segment elevation has a beneficial effect on mortality and major adverse cardiac events. The lower mortality rate and incidence of MACE

emerged with a combination of primary PCI and early clopidogrel administration.

Key words: acute coronary syndrome; clopidogrel; STEMI

Introduction

Current treatment guidelines issued by the European Society of Cardiology (ECS) and the American Heart Association (AHA) recommend that, unless contraindicated, a combination therapy that includes acetyl salicylic acid (ASA) and clopidogrel should be administered to acute coronary syndrome (ACS) patients with non-ST segment elevation (NSTEMI) [1] as well as to ACS patients with STEMI [2]. This treatment is important in preventing short-term mortality after the first event and acts prophylactically for later major adverse cardiac events (MACE), even when no immediate percutaneous coronary intervention (PCI) is performed [3].

A 2008 analysis of data gathered between January 2001 and December 2005 from a large US registry has shown not only that clopidogrel administration to NSTEMI patients immediately after hospital admission significantly reduces in-hospital mortality, but that, even as late as 2005, a considerable portion of patients in the USA were not receiving treatment that fully complied with acknowledged guidelines [4]. Positive clinical benefit for clopidogrel use has been demonstrated for patients undergoing PCI [5]; furthermore, significantly lower 1-year cardiovascular mortality rates were reported in Canada when prescription rates increased after reimbursement authorisation [6]. At the same time, results from a smaller French registry suggest that the clinical outcome after one year does not significantly differ for NSTEMI and STEMI patients [7].

The aim of this study was to obtain further evidence of the clinical benefit of guideline adherence in terms of mortality and MACE in Switzerland, and to investigate compliance with treatment guidelines.

Abbreviations

ACS	Acute Coronary Syndrome
PCI	Percutaneous Coronary Intervention
ASA	Acetyl Salicylic Acid
MACE	Major Adverse Cardiac Event (death, re-infarction, stroke)
MM	medically managed patients (patients not receiving PCI)
STEMI	ST segment Elevation Myocardial Infarction
NSTEMI	Non-ST segment Elevation Myocardial Infarction
OR	Odds ratio

Methods

AMIS (Acute Myocardial Infarction in Switzerland) Plus is a national Swiss registry for patients with acute coronary syndrome (STEMI, NSTEMI, and unstable angina). AMIS is hosted by the Institute of Social and Preventive Medicine at the University of Zurich (now termed AMIS Plus with enhanced data collection). Emphasis is placed on the evaluation of risk factors (family history of coronary artery disease (CAD), diabetes, hypertension, dyslipidemia, smoking), diagnostics, urgent therapy strategies, treatment and long-term outcome of acute coronary syndrome. All data acquisition and analysis tasks are performed in strict accordance with Good Clinical Practice (GCP) guidelines. Details have been described elsewhere [8] and are available from <http://www.amis-plus.ch>. Data are entered in a web-database at the time of hospitalisation. MACE were defined as death, myocardial infarction or re-infarction and stroke. This investigation uses the data from all ACS patients enrolled in the AMIS Plus. The data analysed focused on the impact of clopidogrel, given within 24 hours of admission, on mortality and MACE. Observed treatment regimens were also compared with established treatment guidelines. MACE were defined as composed end points of re-infarction, cerebrovascular events and/or death. The null hypothesis tested was that there is no difference in mortality and MACE because of early clopidogrel administration.

Statistical analysis

The AMIS data centre uses SPSS software for data analysis (SPSS Inc., Chicago, Illinois; Version 17.0). Proportions were compared using Fisher's Exact Test. Odds ratio (OR) with 95% confidence interval were calculated (16). All statistical tests were two-sided. A p value <0.05 was considered significant. A multivariate logistic regression model based on backwards logistic regression methodology was used to determine in-hospital mortality predictors from the following set of variables: age, sex, Killip classes, prior CAD, diabetes current smoking, clopidogrel, primary PCI and resuscitation prior admission.

Results

Demography

The registry included data from 30,243 ACS patients from 76 Swiss hospitals. For 24,463 (81%) of these patients, data on early clopidogrel (<24 h of admission) administration were available (fig. 1). Some 15,525 (51%) of the total cohort were administered clopidogrel within 24h of admis-

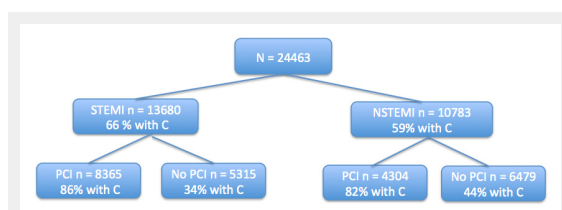


Figure 1

Flow chart of the patient regarding STEMI, NSTEMI and PCI or no PCI and percentage of patients treated with clopidogrel (C).

sion (table 1). Patients receiving early clopidogrel treatment (300 mg loading dose followed by 75 mg/day) were significantly younger (mean age 64 years vs. 69 years, $p <0.001$), there were more smokers (40%, vs. 33%, $p <0.001$), and more males (76 vs. 67%, $p <0.001$). A total of 4.7% of the patients of the early clopidogrel group were in Killip class III and IV versus 10% of the other group ($p <0.001$; table 1). Of note, aspirin was given to all patients and almost 2/3 them had a body mass index above 25. A total of 48% of Swiss patients did not receive primary PCI (including dilation of coronary arteries) and are henceforth termed MM (medically managed) patients.

Mortality and MACE (figure 1)

Early clopidogrel administration is beneficial for 24h mortality, in-hospital mortality and MACE as shown in table 2 and figure 1.

Multivariate analysis shows that some clinical parameters were associated with an increased mortality (table 4). Early clopidogrel administration and PCI were the only treatment that lowered mortality as shown by this analysis.

STEMI patients

In-hospital mortalities were similar but slightly higher for patients with primary PCI (8.0%) alone when compared to early clopidogrel alone (6.8%) ($p = 0.24$). MACE were equally frequent between primary PCI patients without early clopidogrel and patients without primary PCI but early clopidogrel administration (10% versus 9.3%, $p = 0.55$).

Non STEMI patients

Mortality was similar for patients with primary PCI and no clopidogrel (3.4%) and patients without primary PCI and early clopidogrel administration (3.2%, $p = 0.82$). MACE were more frequent in patients without early clopidogrel and 1°PCI versus no primary PCI and early clopidogrel treatment (5.2% versus 4.2%, $p = 0.26$). In both STEMI and non-STEMI the lower mortality rate and incidence of MACE emerged from the group of patients treated with a

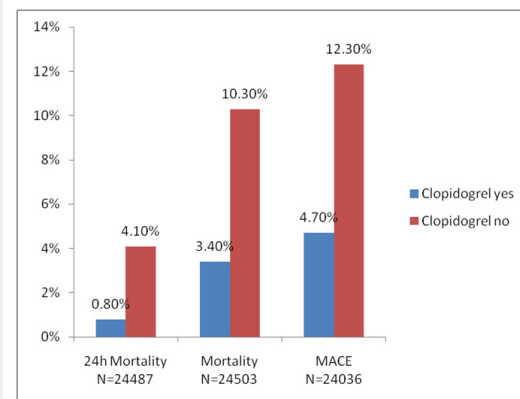


Figure 2

Effect of early clopidogrel administration (within 24h of admission) on 24h mortality, in-hospital mortality, and MACE. The effect of clopidogrel is statistically significant with $p < 0.0001$ in Fisher's exact test in all categories.

combination of primary PCI and early clopidogrel administration (table 3).

Discussion

The AMIS Plus registry with its large database on treatments and outcomes provides a comprehensive picture of AMI management and its development over the years in Switzerland. However, when statistical comparisons are made between therapy dependent outcomes, one must always keep in mind that treatments are not randomised: they

are assigned by the treating physicians in a real-world environment according to an individual assessment based on the patient's particular situation and the facilities offered by the admitting hospital. Baseline comparability of patients receiving different treatments is therefore not ensured, and extensive multivariate analyses for predictors would have to be conducted in order to produce stand-alone valid statistical results. The extent of these differences with respect to early clopidogrel administration in terms of demographic properties, pre-existing pathologies, and previous treatments is shown in table 1. The prevalence of the individual

Table 1: Clopidogrel as immediate therapy in patients admitted for acute coronary syndrome between 2000 and 2008.

	Clopidogrel no (n = 8,978)	Clopidogrel yes (n = 15,525)	p
Gender male	6,006/8,978 (66.9)	11,774/15,525 (75.8)	<0.001
Age in years range mean (SD)	22-101 69.0 (13.6)	21-99 63.6 (12.7)	<0.001
Diabetes	1,972/8,594 (22.9)	2,731/14,914 (18.3)	<0.001
Current smoking	2690/8199 (32.8)	5,878/14,557 (40.4)	<0.001
Hypertension	5,254/8,443 (62.2)	8,619/14,810 (58.2)	<0.001
Dyslipidemia	4,447/7,694 (57.8)	8,259/13,983 (59.1)	0.072
Overweight (BMI >25)	4,633/7,474 (62.0)	8,664/13,202 (65.6)	<0.001
Killip classes n	8,940	15,450	<0.001
I–II	8,040 (89.9)	14,725 (95.3)	
III–IV	900 (10.1)	725 (4.7)	
Regular medication before admission			
Aspirin, ASA	3,603/8,775 (41.1)	5,758/15,117 (38.1)	<0.001
Clopidogrel*	119/2,838 (4.2)	1,262/10,060 (12.5)	<0.001
Oral anticoagulant	808/8,740 (9.2)	665/15,000 (4.4)	<0.001
Beta-blocker	2,867/8,737 (32.8)	4,579/15,032 (30.5)	<0.001
ACE inhibitor or Angiotensin II receptor antagonist	2,862/8,744 (32.7)	4,654/15,046 (30.9)	0.004
Ca-channel blocker	1,248/8,670 (14.4)	1,840/14,952 (12.3)	<0.001
Nitrates	1,324/8,724 (15.2)	1,263/14,978 (8.4)	<0.001
Diuretics	2,279/8,749 (26.0)	2,465/15,016 (16.4)	<0.001
Statins	2,077/8,732 (23.8)	4,237/15,063 (28.1)	<0.001

Table 2a: Isolated effect of early clopidogrel treatment on clinical outcome.

	N	OR	95% CI	p
24 h mortality	24,487	0.20	0.16–0.24	<0.0001
In-hospital mortality	24,503	0.31	0.27–0.34	<0.0001
MACE	24,036	0.35	0.32–0.39	<0.0001

Table 2b: Effect of early clopidogrel treatment, adjusted for age, gender and STEMI.

	N	OR	95% CI	p
24 h mortality	24,447	0.25	0.20–0.31	<0.0001
In-hospital mortality	24,463	0.41	0.36–0.46	<0.0001
MACE	23,996	0.45	0.40–0.49	<0.0001

Table 3: In-hospital mortality and MACE. All proportions are statistically significantly different with respect to early clopidogrel administration ($p < 0.0001$, Fisher's exact test).

In-hospital mortality	STEMI Clopidogrel		NSTEMI Clopidogrel		All Clopidogrel	
	Yes	No	Yes	No	Yes	No
All	370/9,099; 4.1%	568/4,581; 12.4%	154/6,409; 2.4%	352/4,374; 8.0%	528/15,525; 3.4%	926/8,978; 10.3%
1°PCI	246/7,275; 3.4%	87/1,090; 8.0%	62/3,560; 1.7%	25/732; 3.4%	310/10,833; 2.9%	112/1,828; 6.1%
No 1°PCI	124/1,824; 6.8%	481/3,491; 13.8%	92/2,837; 3.2%	326/3,625; 9.0%	218/4,669; 4.7%	813/7,126; 11.4%
MACE	STEMI Clopidogrel		NSTEMI Clopidogrel		All Clopidogrel	
	Yes	No	Yes	No	Yes	No
All	5.7%	14.6 %	3.4%	9.9%	4.7%	12.3%
1°PCI	4.8%	10.0 %	2.8%	5.2%	4.1%	8.1%
No 1°PCI	9.3%	16.1 %	4.2%	10.8%	6.2%	13.5%

risk factors, even smoking, was closely similar to what has been reported in the OPERA study [13], except for hypertension, which was lower in the French investigation (47%). It remains open whether the same blood pressure limits were applied. Our numbers are almost identical for STEMI (29% vs. 29%) and lower for NSTEMI patients (27% vs. 48%) as those reported in the OPERA study [13]. Despite the methodological shortcomings, strong and consistent positive results concerning mortality and, similarly, MACE, cannot possibly be explained by those differences found between the treatment groups cited above. For all ACS patients, the best results are thus achieved with ASA and early clopidogrel, and, when indicated, in combination with primary PCI. Clopidogrel consistently reduces the incidence of mortality as well as MACE for all ACS patients. This was shown when clopidogrel was given in addition to aspirin, like in the CURE [7, 9] CREDO [10] and COMMIT [11] trials. Our results confirm these observations and emphasise the need of early clopidogrel administration and primary PCI. Similar data were recently reported from the GRACE [12] registry with a significant benefit of dual anti-platelet therapy for patients with NSTEMI. These authors, also, conclude to an underuse of this strategy especially in Canadian patients [13]. The observation made in the OPERA [14] study that the outcome after one year is not significantly different for STEMI and NSTEMI cannot be confirmed by the AMIS Plus data.

The finding that NSTEMI patients are less likely to receive early clopidogrel treatment can, to a degree, be explained by the economic pressure exerted by health authorities, and the opinion that these patients are at a lower risk for recurring cardiovascular events. Caution should be applied here in view of the 12-month risk reported in the OPERA study [14]. From 2002 to 2005, early clopidogrel administration in Switzerland was closely similar to the levels reported from the CRUSADE study [4] (i.e., 30–50%). It can be noted with satisfaction that adherence to the recommendations stipulated by the acknowledged treatment guidelines has significantly improved in recent years, and continues to improve with each passing year. However under use of clopidogrel has recently been reported in the GRACE registry [13] showing that efforts should still be made to increase these numbers. Treatment guidelines are, in general, followed better in hospitals with catheter labs (which are usually larger and more centrally located), though guideline adherence has increased with time in recent years in all hospitals.

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Table 4: Independent predictors for in-hospital mortality.

	OR	95% CI	p
Gender	1.01	0.86–1.18	0.93
Killip I	Ref.		
Killip II	2.39	2.00–2.84	<0.001
Killip III	4.52	3.60–5.68	<0.001
Killip IV	17.77	13.42–23.54	<0.001
Prior CAD	1.02	0.87–1.18	0.83
Diabetes	1.30	1.10–1.54	0.002
Current smoking	1.16	0.96–1.39	0.115
Clopidogrel	0.57	0.48–0.69	<0.001
Age	1.07	1.06–1.08	<0.001
Primary PCI	0.70	0.57–0.87	= 0.001
Resuscitation	4.98	3.86–6.44	<0.001

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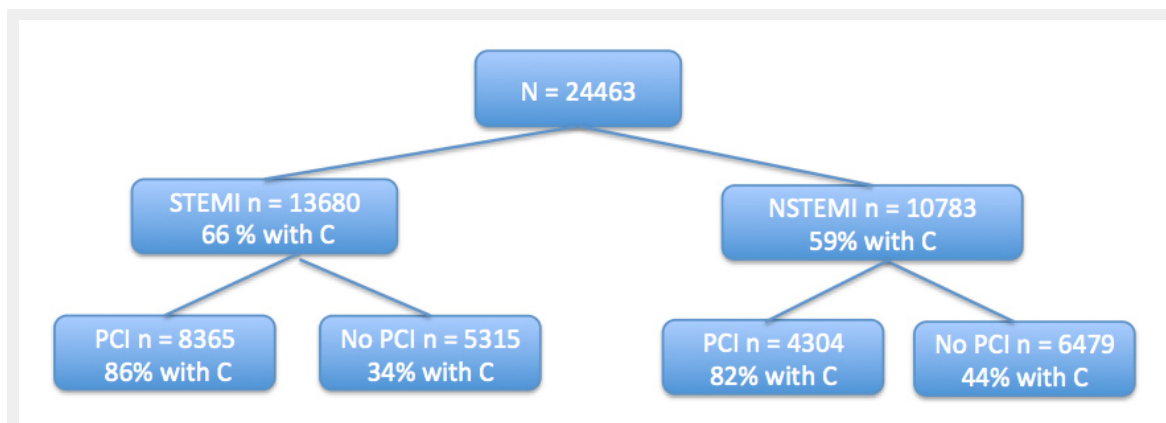
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Correspondence: Professor Jean Christophe Stauffer, MD, Service de cardiologie, Hôpital Cantonal, CH-1700 Fribourg, Switzerland, [jean-christophe.stauffer\[at\]chuv.ch](mailto:jean-christophe.stauffer[at]chuv.ch)

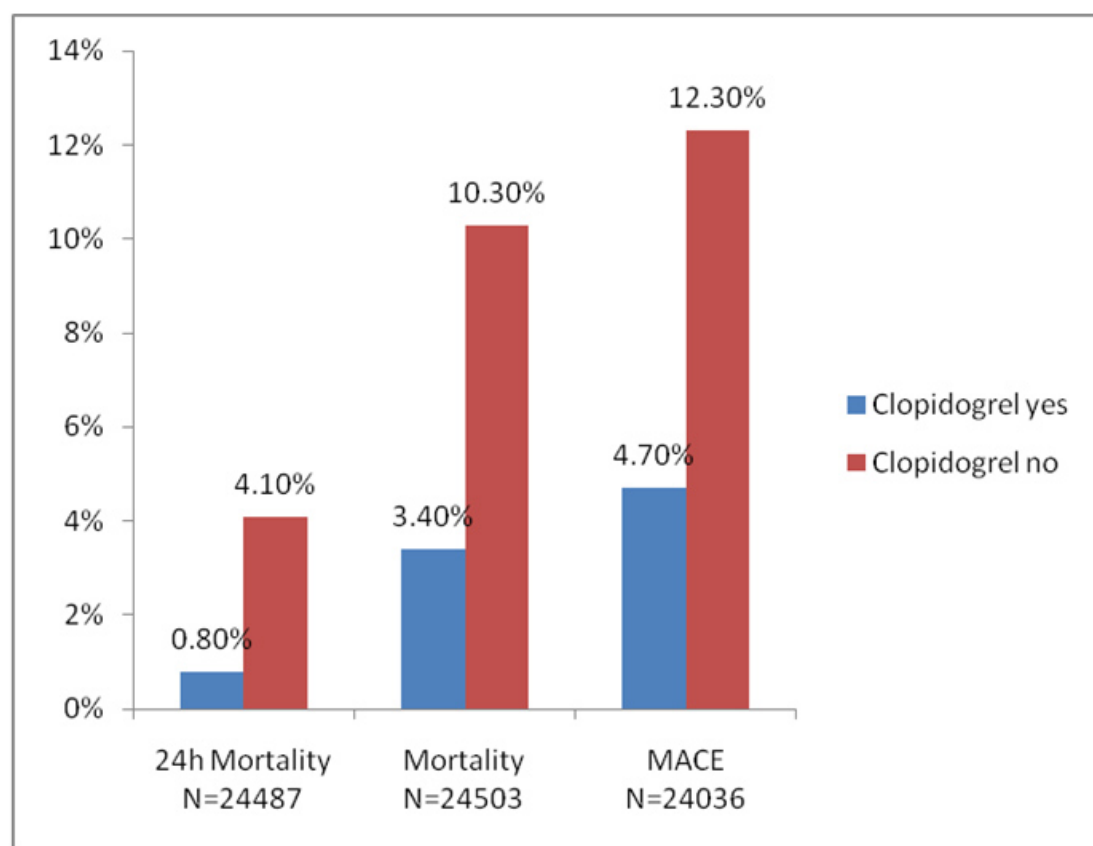
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Figures (large format)

**Figure 1**

Flow chart of the patient regarding STEMI, NSTEMI and PCI or no PCI and wpercentage of patients treated with clopidogrel (C).

**Figure 2**

Effect of early clopidogrel administration (within 24h of admission) on 24h mortality, in-hospital mortality, and MACE. The effect of clopidogrel is statistically significant with $p < 0.0001$ in Fisher's exact test in all categories..